REMARKS/ARGUMENTS

Claims 30-32, 36-38, 40-49, 51-56, 59-60, 65-68, 72-75, 80-114 are in the case.

Reconsideration of this Application and entry of the foregoing amendments are requested. Claims 33-35, 39, 69-71 and 75 have been cancelled, claims 86 to 114 have been added and claims 30-32, 36-38, 40, 45-47, 49, 51 and 66 have been amended in view of the Office Action and to better define what the Applicants consider their invention, as fully supported by an enabling disclosure.

REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 30-45, 47-49, 65-75 and 80-83 have been rejected under 35 U.S.C. § 112, second paragraph as being indefinite because of the use of the term "proteic." This term was deleted from the claims in accordance with the Examiner's opinion. Thus, the rejection is believed to have been overcome.

REJECTION UNDER 35 U.S.C. § 102 AND 103

Claims 30-33, 45-49, 51-52, 54, 55, 59, 60, 65-69, 72 and 80-83 have been rejected as being anticipated by or alternatively obvious over Brown *et al.* ("Brown") under 35 U.S.C. § 102.

The Examiner notes that the sequence disclosed in SEQ ID NO: 3 of Brown is a human Site-1 sequence identical to the amino-acid sequence of SEQ ID NO: 6. He alleges that the wording "variant" in claim 30 embraces a fragment comprising amino acids 187-996 of SEQ ID NO: 6 having additional amino acids of SEQ ID NO: 6 flanking either or both positions 187 and 996. The Examiner alleges that since Brown discusses human and hamster sequences interchangeably and because these sequences are 98% identical one to another, the disclosure of Brown relating to manipulation of, expression of, proteolytic activity of, and substrate recognition of the hamster Ski-1 protease are considered to inherently anticipate the corresponding properties of the human SKI-1 protease. The Examiner further notes that even if the term "variant" were removed from claim 30, the subject matter of this claim would still be obvious over Brown.

Claims 30, 31, 46 and 47 previously containing the wording "variant" were amended to contain the wording "an amino acid sequence from another mammalian species" instead. Additional support for the wording "or an amino acid sequence from another mammalian species" may be found at page 6, lines 4-6.

Soluble SKI

The Examiner further states that Brown discloses a method of producing a soluble Site-1/SKI having an amino terminus at position 187 and discloses a method of cleaving a Site-1/SKI substrate and a composition of SKI. He therefore concludes that claims 30, 45, 46, 65 and 66 are anticipated.

The Examiner is of further opinion that claims 36, 40-44, 72 and 80-83 which relate to nucleic acid encoding a soluble SKI-1, vectors, host cells, and composition thereof are anticipated by Brown at col. 4-5 and 22-33.

Applicants respectfully traverse the rejection as follows.

It is submitted that the description of a soluble hamster SKI-1 having a sequence of amino acids of 187-983 does not anticipate or make obvious a soluble and active human SKI-1 having the amino acids of 187-996 of SEQ ID NO:6. The slightest changes in amino acid sequences may result in a defective folding, activity, specificity or transport and may produce an inactive or defective protein. The Examiner will find enclosed an alignment hamster/human showing the discrepancies between these two sequences.

SKI 14Kda Prosegment

The Examiner further alleges that Brown anticipates claims 31-33 and 67-69 in disclosing a 18-137 fragment having a molecular weight of 14kDa and capable of binding to the SKI-1 protease to which it was bound prior to cleavage.

The Examiner however noted that claim 32 contains allowable subject matter.

Applicants respectfully traverse the rejection as follows.

Claim 31 have been amended to recite a fragment of 17-137 as supported by the disclosure at page 38, lines 7-9 and the human SKI-1 amino acid sequence at page 56 of the specification. Lines 7-9 of page 38 disclose that the

signal peptide is cleaved after the amino acid sequence LVVLLC of the human SKI-1 sequence and it may be seen in the human SKI-1 sequence provided at page 56 of the present specification that the cysteine is the 16th amino acid of the SKI-1 enzyme. Brown indicates that a first cleavage occurs to generate a 23-1052 fragment and a second cleavage occurs to generate a 137–1052 fragment (see col. 10, lines 47-48; col. 16, lines 31-39; Figure 11A). Brown does not therefore disclose a fragment having the sequence of amino acids 17 to 137 of SEQ ID NO: 6.

Claim 32 remains unchanged and should remain allowable in view of the above-stated Examiner's opinion.

The Examiner further alleges that Brown discloses that the 14kDa protein is inhibitory based on the sentence "Cleavage of the NH2-terminal signal sequence of S1P generates S1P-A (amino-acids 23-1052 of SEQ ID NO: 1), which is inactive".

It is not clear to the Applicant how this sentence shows that the 14kDa is inhibitory. According to the Applicant understanding, this wording means that the 23-1052 fragment is inactive. The 14kDa fragment is the 18-137 fragment. It is therefore submitted that Brown does not disclose a 14kDa fragment that is inhibitory. Nevertheless, claims 33 to 35 and all claims depending on them have been cancelled.

SKI substrate

The Examiner is of further opinion that Brown anticipates claims 47-49, claims 51-52, 54 and 55, and claims 59 and 60. He alleges that Brown discloses the use of a soluble SKI-1 produced recombinantly in a cell transfected with a polynucleotide encoding a soluble SKI-1 for cleaving peptide substrates that may be fluorogenically-labelled (ex. SEQ ID NO: 55). This latter peptide allegedly conforms with the motif of claims 51 and 52.

Applicants respectfully traverse the rejection as follows.

Claim 51 now recites a substrate that is not "a sterol-regulatory element-binding protein (SREBP) or a part thereof or a SKI-1 or a part thereof". Support for this wording may be found in previously presented claims 46 and 47. The Applicant recognized at page 46, lines 8 to 11 of the specification that SREBP-2

had already been shown to be a substrate for SKI-1. Since the amino sequence of SEQ ID NO: 55 is a part of a SREBP-2 (see Table VI of the present application, and col. 71, lines 11 to 14), applicant believes that this amendment overcomes the Examiner's objection. Examiner indicated that claims 53 and 56 would be allowable if rewritten in independent form. It is submitted that in view of amended claim 51, claims 53 and 56 may remain unchanged.

Objected subject matter

The Examiner suggested that claims directed to a modified prosegment having increased inhibitory activity as described at pages 44-47 would be found allowable along with nucleic acids encoding same and compositions thereof.

New claims 84-114 cover a prosegment having increased inhibitory activity, methods of use, nucleic acid and compositions thereof. Brown does not disclose such an inhibitory native or recombinant prosegment of about 24kDa. Support for these claims may be found at page 33, lines 1-9; page 42, lines 8-27; p. 43, lines 25-26; page 45, line 20 to page 46, line 3; and Table V at page 49; page 46, lines 26-29; and at page 52, lines 26-31.

The rejections of the original claims are believed to have been overcome by the present amendments, remarks/arguments and the introduction of new claims. From the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order, and such an action is earnestly solicited.

Authorization is hereby given to charge deposit account no. 17-0055 for any deficiencies or overages in connection with this response.

Respectfully submitted,

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